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Reproductive Hormones and Gastrointestinal Motor Disorders: A New Dimension in Therapeutics

A novel approach to the clinical management of disease requires bold new initiatives that are not always in the mainstream of current dogma. The brilliant elucidation of the pathophysiology of peptic ulcer disease opened our minds to new ideas. The impact of the bacterial etiology of ulcer disease changed all of gastroenterology in one sweeping move. The pathophysiology of functional gastrointestinal neuromuscular disorders also requires a new initiative. The classical dogma that functional disorders are psychosomatic or stress-related conditions has lost its momentum. Continued classification and reclassification of the conditions, although interesting to the investigators, also provides limited insight.

Mathias and his colleagues have made a major proposal for our understanding of the functional neuromuscular disorders of the gut. Are these findings valid? Will they stand the test of time? Is it justified to treat our patients based upon these observations?

Several clinical observations suggested for many years that functional motility disorders were linked to ovarian hormones. Firstly, functional gastrointestinal motor disorders are more common in women. Secondly, these conditions worsen with the menstrual cycle, pregnancy, and oral contraceptives. Thirdly, ovarian hormones can be shown to alter gastrointestinal smooth muscle activity in vivo and in vitro. Mathias et al. complete this logic by proposing that disruption of the hypothalamic release of gonadotrophin-releasing hormone (GnRH) by analogs of this hormone may favorably alter symptoms in functional gastrointestinal disorders.

The gastrointestinal community has been somewhat skeptical of the Mathias hypothesis. It is readily acceptable to give antibiotics to eradicate a bacterial infection and to cure ulcers but it is another matter to alter hypothalamic function to treat irritable bowel syndrome. Functional bowel disease has no objective sequelae or measurable pathological lesion to quantify during clinical trials. Many physicians have strong beliefs that functional gastrointestinal disorders are psychosomatic not hormonal in their pathogenesis. Lastly, many of us in gastroenterology consider the hypothalamic-pituitary axis to be a mysterious if not sacred site that we best not tamper with.

Despite these skeptisms, Mathias has made a major step in showing that GnRH analogs may be the new frontier in treatment. The GnRH analogs when given continuously (depot form or daily injection) inhibit production and release of gonadotrophin and reproductive hormone. The GnRH analogs are efficacious in treating endometriosis, polycystic ovary syndrome, precocious puberty, and steroid-dependent malignancies.

The GnRH analogs are not yet FDA approved for the treatment of functional gastrointestinal disorders. Double-blind trials are underway and are promising in their interim analysis. Unblinded observations are quite impressive. If the GnRH analogs are efficacious in relieving symptoms in functional gastrointestinal disorders, is it justified to use them as second- or third-line therapy? The answer is unclear. The analogs are safe but the long-term suppression of gonadotrophin release in an otherwise healthy woman is not known. Can a finite trial of therapy cure the condition? The probability of the latter is not

likely. On the other hand, it is apparent to many clinicians that functional gastrointestinal disorders are a major disabling condition interfering with daily personal and occupational activities in some patients. Should the GnRH analogs be used only in this select group of women?

The introduction of new concepts in pathophysiology and treatment always raise more questions than can be answered immediately. Mathias has made a bold move,

breaking away from the pack. My personal feeling is that his observations are valid and worthy of further study. The elucidation of functional abdominal pain is an important step in medicine. The symptoms are disabling to many otherwise productive individuals. The careful clinical approach to defining the pathway and, thus, its modulation by Mathias is applauded and encouraged. We all await the answer.